REMARKS/ARGUMENTS

By this Amendment, claims 27 and 30 are amended, claims 46-50 are added, and claims 28-29 are cancelled. Claims 39-45 have been withdrawn from consideration pursuant to a restriction requirement. Claims 27, and 30-50 are pending.

Citations to the Specification are directed to U.S. Patent Application Publication No. 2006/0240050 (Surman et al.). Support for the amendments to the claims can be found throughout the Specification as filed, and specifically: support for the limitation "for oral administration" in claim 27 can be found in ¶[0001]; support for the limitation "using a buffer " in claim 27 can be found in original claim 29 and ¶[0068]; support for new claim 46 can be found in ¶[0023]; support for new claim 47 and 48 can be found in ¶[0068]; support for new claim 49 can be found in ¶[0072]; support for new claim 50 can be found in ¶[0076]. No new matter has been added by this amendment.

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

Applicants hereby affirm their prior election with traverse of Group I, claims 27 to 38, reserving their rights under 35 U.S.C. § 121 to file a divisional application for the nonelected claims.

Interview

The Examiner's courtesy in granting an interview to Applicants' representative on May 18, 2010 is gratefully acknowledged. Applicants' separate record of the substance of the interview is incorporated into the following remarks.

Office Communication of 07/26/2010

On July 26, 2010, the Office sent a communication setting forth that:

> The reply filed on 05/17/2010 is not fully responsive to the prior Office Action because of the following omission(s) or matter(s): The Amendment filed on 05/17/2010 has a large "DRAFT" printed on every page of the claims and argument, which makes it difficult to read. Please provide an amendment and argument without the "DRAFT" print.

In response, Applicant points out that this draft document had been provided merely as a point of discussion for the Interview, and was not intended as the Response to the Office Action.

Rejection under 35 USC § 102

Pending claims 27, 30-33, 35, and 36 stand rejected under 35 U.S.C. 102(b) as being anticipated by Eishun (JP 10-175865). This rejection is respectfully traversed.

The Examiner sets forth that Applicant's claims are directed to an aqueous composition comprising of: 0.1-10% of clozapine; buffers, such as sodium phosphate/sodium hydroxide, for a pH of 6-8; and wetting agents, such as propylene glycol. The Examiner argues that Eishun teaches an aqueous composition comprising: 0.5% clozapine (citing the abstract and [0014]); buffers, such as sodium phosphate, for a pH of 7.4 (see abstract); and wetting agents, such as propylene glycol (citing the abstract). The Examiner sets forth that additional disclosures include: 0.9% sodium chloride solution (citing the abstract), which allegedly reads on water; and emulsified (citing [0013]); suspending agents, such as carboxymethyl cellulose (citing [0011]).

However, in Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987) (MPEP 2131), the CAFC set forth that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference". In the instant case, not every element of the claims is present in the Eishun (JP 10175865) reference.

The instant claims are directed to a physicochemically stable aqueous composition for oral administration comprising clozapine in suspension and a buffer, wherein the pH of the composition is maintained within the range of about 6 to about 11. In contrast to the claimed clozapine composition for oral administration, the Eishun (JP 10175865) reference describes a solution (i.e., not a suspension) intended for application to the eye (i.e., not oral administration) of up to 0.5% clozapine. The Eishun reference teaches formulations for eye drops. In this reference clozapine (at levels up to 0.5%) is dissolved in 0.9 % NaCl solution. Clozapine is dissolved in 0.9 % sodium chloride solution and then added to a viscosity modifier. These are not true suspensions in which clozapine particles are suspended in a matrix.

It is known in the art that suspensions may cause irritation when applied to the eye, as disclosed in U.S. Patent No. 4,558,066 (Waterbury), which teaches (col. 22, lines 58-61):

> Suspensions have the advantage of more extended action and the disadvantage that it is difficult to avoid the presence of a few particles which are large enough to cause irritation.

In addition, it is known in the art that clozapine is unsuitable for formulating as a solution due to its very low solubility. While a solution of clozapine may be appropriate for use in the eye, due to the sensitivity of the tissues in the eye and the necessity of using low doses of clozapine, the low solubility in water makes a solution of clozapine impracticable for oral administration due to the larger dose necessary for oral administration. For example, according to the Physicians Desk Reference (Physicians' Desk Reference. 55th ed. Montvale, NJ: Thomson PDR; 2001:2155-2159), a target dose of clozapine is 300 mg – 600 mg / day, and may reach as high as 900 mg/day (see PDR at 2158). As disclosed in the Merck Index (Merck Index. 13th ed. Merck: Whitehouse Station, NJ, 2001; 2448), the weight/weight solubility at 25°C in water is <0.01% (i.e., < 0.1 mg/ml). The pH of water is around neutral; therefore the solubility in a solution at pH 7 would be very similar to that in water.

So, using the solution of Eishun, for the target dose a patient would be required to drink 3000 - 6000 mL of solution (i.e., 3 - 6 liters) and a patient on 900 mg of clozapine per day would be required to drink 9000 mL (i.e., 9 liters), which is impracticable.

The Eishun reference does not teach every element of the claims. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Rejection under 35 USC § 103

Pending claims 27, 30-38 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Eishun (JP 10-175865) in view of Honma et al (US 6,569,903), Ali et al (US 5,521,222) and Horlington (US 4,425,346). This rejection is respectfully traversed.

The Examiner sets forth that Eishun teaches an aqueous composition comprising of: 0.5% clozapine (citing the abstract and [0014]); buffers, such as sodium phosphate, for a pH of 7.4 (see abstract); and wetting agents, such as propylene glycol (citing the abstract). Additional disclosures include: 0.9% sodium chloride solution (citing the abstract), which allegedly reads on water; emulsified (citing [0013]); and suspending agents, such as carboxymethyl cellulose (citing [0011]).

The Examiner admits that Eishun does not teach using preservatives, such as methylparaben; glycerine, NaOH buffer, and xanthan gum, but argues that Honma teaches ophthalmic compositions with commonly used preservatives, such as methyl-hydroxybenzoate (citing '903 at col. 7, line 62-65), which is methylparaben; isotonizing agents, such as glycerine

and propylene glycol and polyethylene glycol (citing '903 at col. 7, line 55-59); and sodium hydroxide buffers for adjusting pH (citing '903 at col. 8, line 40-42).

The Examiner argues that Ali teaches ophthalmic compositions commonly use preservatives, such as methylparaben (citing '222 at col. 3, line 5-8); tonicity adjusting agent, which reads on isotonizing agents disclosed in Honma, include glycerine and propylene glycol in the amount of 0.1-10% (citing '222 at col. 3, line 13-16); NaOH buffering to a pH of 7.2 (citing '222 at col. 3, line 35), and that Horlington teaches ophthalmic compositions commonly use suspending agents, such as carboxymethyl cellulose and xanthan gum (citing '346 at col. 6, line 15-18).

The Examiner argues that it would have been obvious to the person of ordinary skill in the art at the time the invention was made to incorporate preservatives, such as methylparaben; glycerine, NaOH buffer, and xanthan gum into Eishun's composition, alleging that the person of ordinary skill in the art would have been motivated to make those modifications, because the preservatives would extend the shelf-life of the composition; the glycerine and xanthan gum are functional equivalents of propylene glycol and carboxymethyl cellulose used in Eishun; and adjusting pH using acid/base buffers, such as NaOH, are well-known. The Examiner argues that the person of ordinary skill in the art reasonably would have expected success because these are all commonly used ingredients in ophthalmic compositions.

The Examiner admits that the references do not specifically teach adding the ingredients in the amounts claimed, but argues that the amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Further that optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ and reasonably would expect success. The Examiner argues that it would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient to add in order to best achieve the desired results. The Examiner argues that, absent some demonstration of unexpected results from the claimed parameters, this optimization of ingredient amount would have been obvious at the time of Applicant's invention.

However, the claims are patentable over the combination of Eishun in view of Honma, Ali, and Horlington at least for the following reasons. The framework for the objective analysis

for determining obviousness under 35 U.S.C. 103 is stated in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Obviousness is a question of law based on underlying factual inquiries. The factual inquiries enunciated by the Court are as follows: (A) Determining the scope and content of the prior art; and (B) Ascertaining the differences between the claimed invention and the prior art; and (C) Resolving the level of ordinary skill in the pertinent art. To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385 (CCPA 1970). MPEP 2143.03. It is important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. (*KSR v Teleflex*, 12 S.Ct. 1727, 1740 (US 2007)).

The claims are directed to a physicochemically stable aqueous composition for oral administration comprising clozapine in suspension and a buffer, wherein the pH of the composition is maintained within the range of about 6 to about 11. As set forth above, in contrast to the claimed clozapine suspension composition for oral administration, the Eishun (JP 10175865) reference describes a solution (not a suspension) intended for application to the eye (not oral administration) of up to 0.5% clozapine, and it is known in the art that clozapine is unsuitable for formulating as a solution for oral administration due to its very low solubility. As set forth above, the Eishun reference is not practical for making an oral solution, and the deficiencies of the Eishun reference are not addressed by the combination with the Honma, Ali, and Horlington references, because the instant claims are directed to stable oral formulations of clozapine. The cited references teach formulations for either eye drops/eye gel or ointment. In these references, clozapine (at levels between 0.0001 and 5%, more likely 0.1 to 0.5%) is dissolved in 0.9% NaCl solution. Clozapine is dissolved in 0.9% sodium chloride solution and then added to a viscosity modifier. These are not true suspensions in which clozapine particles are suspended in a matrix.

The Honma reference discloses ('903 at col. 2. lines 16-22, emphasis added):

> It is an object of this invention to provide an ophthalmic composition with as low side effects on the heart as possible, more specifically, to provide a composition whose side effects on the heart are sufficiently suppressed and which is capable of promoting tear secretion. It is another object of this invention to provide a composition which is able to increase protein

concentration secreted in tears.

Accordingly, the Honma reference does not teach or suggest an oral suspension formulation of clozapine.

With regard to the Ali patent, it discloses ('222 at col. 1, lines 40-46, emphasis added):

> This invention relates to ophthalmic pharmaceutical vehicles and compositions comprising the vehicle and a pharmaceutically active drug in which the vehicle comprises a charged polymer and oppositely charged electrolytes or molecules, hereinafter referred to collectively as "electrolytes", which can be administered as a drop and upon instillation, gel.

Accordingly, the Ali patent does not teach or suggest an oral clozapine suspension formulation.

The deficiency of the Eishun, Honma and Ali patents are not cured by combination with the Horlington patent. The Horlington patent discloses ('346 at col. 1, lines 18-25, emphasis added):

> Clearly it would be desirable to provide an agent which could be applied topically to treat ocular hypertension and glaucoma without an unacceptable level of such side effects. It has now been found that the optical administration of tetraazabicyclic compounds to the eye can reduce the intra-ocular pressure therein without producing an unacceptable level of side effects such as pupil constriction.

Accordingly, the Horlington patent does not teach or suggest an oral formulation of clozapine in suspension.

In addition, the Examiner must determine what is "analogous prior art" for the purpose of analyzing the obviousness of the subject matter at issue. MPEP 2141.01(a). Here, the ophthalmic solutions of the Eishun, Honma, Ali, Horlington references are not analogous art to the claimed suspension of clozapine for oral administration. It is known in the art that suspensions may cause irritation when applied to the eye, as disclosed in U.S. Patent No. 4,558,066 (Waterbury), which teaches (col. 22, lines 58-61):

> Suspensions have the advantage of more extended action and the disadvantage that it is difficult to avoid the presence of a few particles which are large enough to cause irritation.

Therefore, oral suspensions are not analogous to ophthalmic solutions.

In addition, the claims are directed to oral suspensions, not formulations for protection against glaucoma. The claimed product is an oral composition for the treatment of psychotic patients. Treatment of psychotic patients using the eye drops as taught in the cited references would require administration of about 70 ml of a 0.5 % solution through the eye to reach therapeutic levels of about 350 mg/day. This is not achievable, and the patient would not be compliant.

In addition, since none of the Eishun, Honma, Ali, Horlington references disclose or suggest a physicochemically stable aqueous composition for oral administration comprising clozapine in suspension, wherein the pH of the composition is maintained in the range of about 6 to about 11, the combination of the patents does not and cannot disclose or suggest these limitations.

Furthermore, there is no motivation for one of skill in the art to alter the teachings of the Eishun reference or the Honma, Ali, or Horlington patents to arrive at the claimed method, and no reasonable expectation of success. The combination of the Eishun reference and the Honma, Ali, or Horlington patents does not teach or suggest all the claim limitations, specifically the combination does not teach or suggest stable oral suspension formulations of clozapine, and therefore, since the combination of the references does not disclose or suggest these limitations, there is no motivation to combine the references to reach these limitations, and no expectation of success.

Unexpected Results and Comparison to Reference Cited in Interview

Applicant has performed further experiments which demonstrate the unexpected stability of the claimed composition. "A greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness ... of the claims at issue." In re Corkill, 711 F.2d 1496, 226 USPQ 1005 (Fed. Cir. 1985). Evidence of the unexpected stability of the claimed composition is set forth in the Declaration of Sharon Ferguson, submitted herewith.

In addition, in the Interview, the Examiner referred to the Ramuth reference (Ramuth et al. Pharm Journal 257:190-191, 1996, cited on the IDS submitted herewith). This reference discusses compounding clozapine into liquid preparations using Guy's Pediatric Base. However, the reference only tested stability for 18 days, as opposed to the at least 14 month stability of the claimed composition. The Specification teaches that clozapine in such typical solutions is

readily susceptible to hydrolysis (see ¶[0006]).

Applicant was unable to obtain a quantitative formulation for Guy's Pediatric Base and therefore was unable to test it for stability. However, Applicant has performed a comparison of a clozapine liquid preparation using Clatterbridge Hospital Base, which contains 1% xanthan gum and water, but contains no buffers or preservatives, with a physicochemically stable aqueous composition for oral administration comprising clozapine in suspension and a buffer, wherein the pH of the composition is maintained within the range of about 6 to about 11 (see the Declaration of Sharon Ferguson under 37 CFR § 1.132, submitted herewith).

In the comparison, a clozapine liquid preparation was prepared using Clatterbridge Hospital Base, comprising Clopine 100 mg Tablets (CS 116) and also Clozaril 100 mg Tablets - Australian Ref Product (CS117) were ground and put into the Clatterbridge Hospital Base. These samples were stored them at both 5°C and 40°C, and a Relative Humidity of 75%. (See Declaration of Sharon Ferguson at ¶[10]).

The Results show that for both the CS 116 and 117 samples had a bad odor after 1 month at 40°C and 75% Relative humidity. CS 116 formed crystals after 1 month at 40°C and 75% Relative humidity and no further testing was performed. CS117 after 2 months at 40°C and 75% Relative humidity had a pH drop and a bad odor. (See Declaration of Sharon Ferguson at ¶¶[12-13]).

As comparison, Applicant has prepared a physicochemically stable aqueous composition for oral administration comprising clozapine in suspension and a buffer, wherein the pH of the composition is maintained within the range of about 6 to about 11, as claimed, and tested the stability. As shown in the Declaration, stability results obtained show acceptable stability up to 24 months at 25°C/60% RH and 6 months 40°C/75% RH. Accordingly, the claimed composition is significantly more stable than would be expected for a clozapine liquid solution preparation. (See Declaration of Sharon Ferguson at ¶[14-19]).

In addition, physicochemically stable aqueous composition for oral administration comprising clozapine in suspension manufactured by Douglas has been approved for sale in Ireland. (See Declaration of Sharon Ferguson, Exhibit B). This is the Product Authorization as approved by the Irish Medicines Board, which shows that the claimed composition has been approved with a stability of 24 months. (See Declaration of Sharon Ferguson at ¶¶[20-22]).

Accordingly, the claimed composition is significantly more stable than would be expected for a clozapine liquid preparation prepared according to the combination of the Eishun, Honma, Ali, Horlington references. In addition, the claimed composition is significantly more stable than would be expected for a clozapine liquid solution preparation.

Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

* * *

For at least the reasons set forth above, it is respectfully submitted that the above-identified application is in condition for allowance. Favorable reconsideration and prompt allowance of the claims are respectfully requested.

Should the Examiner believe that anything further is desirable in order to place the application in even better condition for allowance, the Examiner is invited to contact Applicant's undersigned attorney at the telephone number listed below.

Respectfully submitted,

CAESAR, RIVISE, BERNSTEIN,
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August 10, 2010

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Please charge or credit our Account No. 03-0075 as necessary to effect entry and/or ensure consideration of this submission.